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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICEIn re Application of
Scherer et al.

Application No. 09/914,478

Filed: 08/24/2001

Title: Method for producing (1,1':4',1'') Terphenyl Compounds

Docket: 1999DE304

Examiner: Zucker, P. A.

Art Unit: 1621

DECLARATION UNDER 37 CFR 1.132Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Dr. Stefan Scherer, declare I am a citizen of Germany, residing in the city of Böttelborn;

I am a co-inventor of the above-named Application;

I have a PhD in Chemistry from the University of Frankfurt in Germany in 1995;

I was employed by Hoechst Aktiengesellschaft from 1996 to July 1997, and from July 1997 until the present I continued my employment with Clariant GmbH, as a research Chemist,

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I am well acquainted with the development and commercialization of organic chemicals and aromatic organic chemicals and have been employed in this technology area since 1997. Since that time, and as part of my regular job duties, I have been responsible for the basic development of many organic chemical compounds and new syntheses for known organic compounds and aromatic organic compounds.

Applicant's invention is directed to an improved synthesis for terphenyl compounds. The main reference that the office bases its rejection on is the US equivalent of the WO 94/25050, which was discussed, extensively in our patent application. On pages 1 and 2 of the US application Applicants state:

WO 94/25050 describes a multistage method for producing 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid (cf. pages 28 and 29 part A, part B and part C).

In a first step, 4'-bromo-4-hydroxybiphenyl is reacted with an n-pentyl halide to give the corresponding 4'-bromo-4-n-pentoxybiphenyl. The 4'-bromo-4-n-pentoxybiphenyl is reacted in a second step with n-butyllithium at -78°C to form, by transmetalation, 4'-lithium-4-n-pentoxybiphenyl which, in another step likewise at -78°C, is reacted with triisopropyl borate. Hydrolysis and work-up result in 4'-n-pentoxybiphenyl-4-boronic acid, which is reacted in further steps with 4-iodobenzoic acid in a standard Suzuki coupling. The 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid is obtained as crude product which is purified by chromatography on silica gel.

WO 94/25050 states yields only for the stages (part A and part B) up to formation of 4-(4-n-pentoxyphenyl)phenylboronic acid. There is no statement of yield in part C, which relates to the production of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid.

Then on page 18 and 19 of the US Application sets forth:

Comparative examples according to WO 94/25050 for preparing 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid

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Comparative example 1**Preparation of 4'-n-pentoxybiphenyl-4-boronic acid from 4-bromo-4'-n pentoxybiphenyl**

31.9 g (0.1 mol) of 4-bromo-4'-n-pentoxybiphenyl are dissolved in 640 ml of tetrahydrofuran under a nitrogen atmosphere and cooled to -78°C , and 67 ml (0.11 mol) of 15% strength solution of n-butyllithium in hexane are added dropwise over the course of 2 hours. During this, the internal temperature is kept in the range from -78°C to -65°C . After the addition is complete, the thick milky suspension stirred at -78°C for a further 15 minutes and then 25.5 ml (0.11 mol) of triisopropyl borate are added dropwise at -78°C over the course of 15 minutes. After the borate addition is complete, the resulting clear solution is stirred at -78°C for 15 minutes.

This is followed by a removal of the cooling bath and, after 40 minutes, the solution is adjusted to pH 2 with 100 ml of 2N hydrochloric acid. The phases are separated, the organic phase is washed with water and saturated brine and then the solvents are removed by distillation with 5 addition of 200 ml of water. The precipitated solid is filtered off and dried. 25.8 g (91%) of 4'-n-pentoxybiphenyl-4-boronic acid of melting point $148-150^{\circ}\text{C}$ are obtained.

Comparative example 2**Preparation of 4"-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid from 4'-n-pentoxybiphenyl-4-boronic acid**

25 g (0.088 mol) of 4'-n-pentoxybiphenyl-4-boronic acid and 21.8 g (0.088 mol) of 4-iodobenzoic acid are suspended under an inert gas atmosphere in a mixture of 270 ml of ethanol, 750 ml of toluene and 132 ml of a 2M sodium carbonate solution and, after addition of 5.08 g (4.4 mmol) of tetrakis(triphenylphosphine)palladium, heated under reflux for 18 hours. The gray-brown mixture is cooled, acidified and extracted

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with ethyl acetate. The organic phase is washed with water and saturated brine, dried (sodium sulfate) and filtered through Celite. Removal of the solvent results in 1.2 g of a solid which, however, according to HPLC analysis (comparison with reference substance) contains no 4"-n-pentoxy [1,1':4',1'']-terphenyl-4-carboxylic acid at all.

Evidently, no 4-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid has been formed by the synthetic route indicated in WO 94/25050.

Unexpectedly, in view of the prior art, using the process of the present invention this compound can be prepared with good yields and high purity as set forth in the Application on pages 14-18:

Preparation of 4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid from 4-n-pentoxyphenylboronic esters

Example 5

Preparation of 4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid

162 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 129 g of glycol ester of 4-n-pentoxyphenyl boronic acid and 79.5 g of sodium carbonate into 1.5 l of ethylene glycol and, while stirring vigorously, 350 mg of PdC12(PPh3)2 are added and the mixture is stirred at 80°C for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 150 g of 37% strength sulfuric acid and 1 000 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 141 g (78%) of 4"-n-pentoxy [1,1':4',1'']-terphenyl-4-carboxylic acid with a purity of > 99%.

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Example 6**Preparation of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid**

32.4 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 25.8 g of glycol ester of 4-n-pentoxyphenylboronic acid and 15.9 g of sodium carbonate into 300 ml of ethylene glycol and, while stirring vigorously, 70 mg of PdC12(PPh3)2 are added, and the mixture is stirred at 120°C for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 30 g of 37% strength sulfuric acid and 200 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 25.2 g (70%) of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid with a purity of > 99%.

Example 7**Preparation of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid**

32.4 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 25.8 g of glycol ester of 4-n-pentoxyphenylboronic acid and 15.9 g of sodium carbonate into 300 ml of ethylene glycol and, while stirring vigorously, 18 mg of PdC12 and 26.6 mg of PPh3 are added, and the mixture is stirred at 80°C for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 30 g of 37% strength sulfuric acid and 200 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 24.1 g (67%) of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid with a purity of > 99%.

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Example 8**Preparation of 4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid**

162 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 129 g of glycol ester of 4-n-pentoxyphenylboronic acid and 79.5 g of sodium carbonate into 1.5 l of ethylene glycol and, while stirring vigorously, 17.5 ml of a $\text{Pd}(\text{dba})_2$ solution are added and the mixture is stirred at 80°C for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 150 g of 37% strength sulfuric acid and 1,000 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 132 g (73%) of 4"-n-pentoxy terphenyl-4-carboxylic acid with a purity of > 99%.

Preparation of the $\text{Pd}(\text{dba})_2$ solution:

Under an inert gas, 1.47 g of sodium tetrachloropalladate are suspended in 175 ml of ethylene glycol and heated to 60°C and, after addition of 3.65 g of dibenzylidene acetone (dba), stirred at 60°C for 15 minutes. This is followed by addition of 7.5 g of sodium acetate and stirring at room temperature for a further 60 minutes. The dark-colored solution is employed as such.

Example 9**Preparation of 4"-n-pentoxy-[1,1':A',1'']- terphenyl-4-carboxylic acid**

20.1 g of 4'-iodobiphenyl-4-carboxylic acid, 13.1 g of sodium carbonate and 21.4 g of glycol ester of 4-n-pentoxyphenylboronic acid are introduced into 260 g of dimethyl sulfoxide (DMSO) and, after addition of 160 mg of $\text{PdCl}_2(\text{PPh}_3)_2$, heated at 100-110°C for 2 hours. The solid is filtered off at 40°C, washed with dimethyl sulfoxide and suspended in 100 ml of water. It is then heated to 80°C, and 47 g of 37% strength

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sulfuric acid are added dropwise over the course of 1 hour. The mixture is stirred at 80°C for a further 30 minutes, cooled at 40°C and filtered. Drying and crystallization from dimethylacetamide results in 18 g (81%) of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid with a purity of > 99%.

Example 10

Preparation of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid

32.4 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 25.8 g of glycol ester of 4-n-pentoxyphenylboronic acid and 15.9 g of sodium carbonate into 300 ml of methanol/ethylene glycol 9:1 and, while stirring vigorously, 70 mg of $\text{PdCl}_2(\text{PPh}_3)_2$ are added, and the mixture is stirred under reflux for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 30 g of 37% strength sulfuric acid and 200 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 28.9 g (80%) of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid with a purity of > 99%.

Example 11

Preparation of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid

162 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 155 g of 2,2-dimethylpropane-1,3-diol ester of 4-pentoxyphenylboronic acid and 79.5 g of sodium carbonate into 1.5 l of ethylene glycol and, while stirring vigorously, 350 mg of $\text{PdCl}_2(\text{PPh}_3)_2$ are added and the mixture is stirred at 80°C for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 150 g of 37% strength sulfuric acid and 1000 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then

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recrystallized from dimethylacetamide. This affords after drying 43.2 g (24%) of 4'-n-pentoxyterphenyl-4-carboxylic acid with a purity of > 99%.

Example 12

Preparation of 4'-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid from 4-n-pentoxyphenylboronic acid

34.1 g (0.1 mol) of 95% pure 4'-iodobiphenyl-4-carboxylic acid are introduced together with 26 g (0.125 mol) of 4-n-pentoxyphenyl boronic acid, 15.9 g (0.15 mol) of sodium carbonate and 70 mg of bis(triphenylphosphine)palladium dichloride ($\text{PdCl}_2(\text{PPh}_3)_2$) into 300 ml of DMSO. The suspension is stirred at 80°C for 6 hours, the solid is filtered off, introduced into water, acidified with 37% strength sulfuric acid, heated at 95°C for 30 minutes and filtered again. Recrystallization from dimethylformamide (DMF) results in 22.1 g (61%) of 4'-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid.

Preparation of methyl 4'-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylate from methyl 4'-iodobiphenyl-4-carboxylate

Example 13

Preparation of methyl 4'-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylate

33.8g (0.1 mol) of methyl 4'-iodobiphenyl-4-carboxylate are introduced together with 29.3 g (0.125 mol) of glycol ester of 4-n-pentoxyphenylboronic acid, 70 mg of bis(triphenylphosphine)palladium dichloride and 15.9 g (0.15 mol) of sodium carbonate into 300 ml of DMF and stirred at 80°C for 12 hours. After filtration and washing with water, the dried residue is recrystallized from DMF. This affords 20.5 g (45%) of methyl 4'-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylate of melting point 248°C.

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In light of Applicants comparative examples and the experimental data on Applicants process Applicants' respectfully request that the obvious rejection to USP 5,948,753 Balkovec, which was discussed throughout Applicants' application in its European form, as WO 94/25050, be withdrawn and the claims allowed.

The under signed declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

28.1.2003

Date



Dr. Stefan Scherer
Clariant GmbH